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## MicroRNAs–Based Imaging Techniques in Cancer Diagnosis and Therapy

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### ABSTRACT

Cancer is one of the most serious global health concerns in different populations. Several studies indicated that there are many potentially promising cellular and molecular targets for cancer therapy within cancer cells and their microenvironment. Among different cellular and molecular targets involved in cancer pathogenesis, microRNAs (miRNAs) are well known as key targets for cancer therapy. miRNAs are one of main classes of non-coding RNAs. These molecules play important roles in different critical processes of cancer pathogenesis. Hence, this makes miRNAs as a suitable tool for cancer diagnosis and therapy. There are different approaches for monitoring miRNAs in cancer patients. Some conventional approaches including next-generation sequencing, real-time polymerase chain reaction (PCR), northern blotting, and microarrays could be used for assessment of miRNAs expression. Some studies revealed that the utilization of these approaches associated with various limitations. Recently, it has been revealed that molecular imaging techniques are powerful tools for monitoring of different cellular and molecular targets involved in various diseases such as cancer. These techniques help investigators to investigate and monitor miRNAs functions through assessing different targets by fluorescent proteins, bioluminescent enzymes, molecular beacons, as well as various nanoparticles. Therefore, utilization of molecular imaging techniques could assist investigators to better monitor and more effectively treat patients during different phases of malignancy. Here, we give a review on the current state of miRNAs-based imaging techniques in cancer diagnosis and therapy. *J. Cell. Biochem.* 9999: 1–8, 2017. © 2017 Wiley Periodicals, Inc.

**KEY WORDS:** MOLECULAR IMAGING; MicroRNA; CANCER; DIAGNOSIS; THERAPY

To date, cancer has been emerged as one of main health problems in worldwide [Faghihloo et al., 2016; Mirzaei et al., 2016a–c]. Despite of recent advances in cancer therapy (such as gene therapy, cell therapy, and molecularly-targeted therapies), this disease has remained as one of the major public health issues worldwide [Mirzaei et al., 2016d–f, 2017a; Mohammadi et al., 2016a]. Hence, the identification of new targets and molecules involved in cancer, from initiation to

progression and treatment, could contribute in understanding of the pathways involved in cancer pathogenesis [Arabpour et al., 2016; Mirzaei et al., 2016; Simonian et al., 2016]. These finding could lead to development of new and effective treatments in this field. One of the most important mediators in cancer pathogenesis is microRNAs (miRNAs) [Fathollahzadeh et al., 2016; Mohammadi et al., 2016b; Gholamin et al., 2017; Mirzaei et al., 2017b; Moridikia et al., 2017].

Conflicts of interest: None.

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Manuscript Received: 21 March 2017; Manuscript Accepted: 22 March 2017

Accepted manuscript online in Wiley Online Library (wileyonlinelibrary.com): 29 March 2017

DOI 10.1002/jcb.26012 • © 2017 Wiley Periodicals, Inc.

MiRNAs are well known as a class of non-coding RNAs which play key roles in a wide range of biological processes including development, cellular differentiation, proliferation, and apoptosis in living organisms [Ryoo et al., 2013; Gholamin et al., 2016; Rashidi et al., 2016]. The lengths of these molecules are almost ~22 nucleotides [Mirzaei et al., 2016b]. Several studies indicated that miRNAs have a central role in pathogenesis of various diseases such as cancer [Gholamin et al., 2017; Mirzaei et al., 2017a; Moridikia et al., 2017]. Hence, detection and profiling of these molecules could contribute to the better understanding of cancer pathogenesis and, thereby, developing more precise strategies for early detection and/or treatment of cancer [Zubakov et al., 2010; Salarini et al., 2015; Gholamin et al., 2016; Mirzaei et al., 2016c]. So far, various conventional approaches such as microarray and RT-PCR have been used for miRNAs detection in different living systems [Li and Ruan, 2009; Momin et al., 2009; Hernandez et al., 2013]. These approaches are associated with some limitations. For example, these approaches are time-consuming and laborious and required to fix or lyse the cells and thus cannot monitor dynamic functions of miRNAs in living cells and organisms (In vivo) [Fang et al., 2006; Lu and Tsourkas, 2009; Ryoo et al., 2013]. To overcome the limitations, developing new and more efficient, particularly noninvasive repeated quantitative, methods are the most highly demanded. Recently, some imaging techniques have been emerged as effective tools for monitoring of miRNAs [Wang et al., 2009; Hernandez et al., 2013]. Imaging techniques are well known as powerful tools in monitoring of various targets and genes in many diseases such as cancer [Wang et al., 2009; Hernandez et al., 2013]. These techniques could provide new avenue in diagnosis and treatment of cancer. Various imaging techniques such as magnetic resonance imaging (MRI), florescence imaging, and bioluminescence imaging (BLI) could be used for monitoring and detection of miRNAs in patients with cancer [Wang et al., 2009; Hernandez et al., 2013]. In the present review, we will not only focus on a variety of miRNAs involved in cancer pathogenesis but also highlight some recently developed

imaging methods which assist investigators to detect miRNAs in a high throughput profiling and noninvasive repeated quantitative manner in preclinical and clinical cancer studies.

## MicroRNA AND CANCER

MiRNAs are one of main class of non-coding short RNAs that are highly conserved [Mirzaei et al., 2016e,b; Mohammadi et al., 2016b]. These RNAs regulate gene expression at different levels (protein and RNA) [Rashidi et al., 2017; Salarini et al., 2015]. MiRNAs have multiple biological roles in different processes within living organisms [Mirzaei et al., 2017a; Rashidi et al., 2017]. Figure 1 illustrate a scheme of miRNA biogenesis. Multiple lines of evidence indicated that miRNAs play important roles in initiation and progression of various cancers [Mirzaei et al., 2016f,g; Mohammadi et al., 2016b]. These molecules regulate different cellular and molecular pathways including Wnt, Notch, TGF- $\beta$  and play putative roles in epithelial-mesenchymal transition (EMT). It is plausible that some expression aberrations of miRNAs might lead to initiation and/or development of a variety of cancers [Mirzaei et al., 2016g,h; Mohammadi et al., 2016b] (Table I). Various studies have been revealed that miRNAs could be used as diagnostic, prognostic and therapeutic biomarkers for various cancers. Therefore, monitoring of miRNA expression patterns can assist the elucidation of the biogenesis and biological function of miRNAs in different phases of cancers.

## MicroRNA AND MOLECULAR IMAGING IN CANCER

The miRNAs are known to regulate the expression of genes involved in many cellular/and molecular pathways. The aberration of these

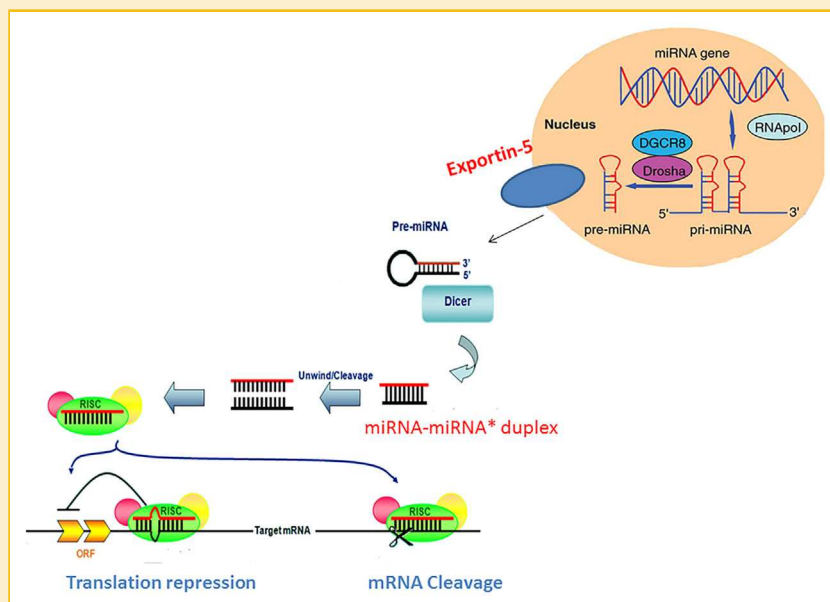


Fig. 1. A scheme of miRNA biogenesis.



TABLE I. Various MiRNAs Involved in Cancer Pathogenesis

Type of cancer	miRNA	Expression in cancer	Target gene	Stage/patient sample	Citation
Melanoma	miR-200c	Down regulation	ZEB1, DEF1, Nii-2-A	I, II, III, IV/41	Xu et al. [2012]
	miR-211	Down regulation	MITF, AP1S2, SOX11, IGFBP5	I, II, III, IV/41	Xu et al. [2012]
	miR-205	Down regulation	E2F1, E2F5	I, II, III, IV/41	Xu et al. [2012]
	miR-203	Down regulation	E2F3	I, II, III, IV/41	Xu et al. [2012]
	miR-33a	Up regulation	Pim-1, CDK6, cyclin D1	I-III/140	Friedman et al. [2012]
	miR-33a	Up regulation	p53, c-Myc	IIIB, IIIC, IV/59	Segura et al. [2010]
Lung	miR-193b	Up regulation	MAPK, PI3K-AKT, p53, ErbB	I, II/107	Nadal et al. [2015]
	miR-301	Up regulation	MAPK, PI3K-AKT, p53, ErbB	I, II/107	Nadal et al. [2015]
	miR-141	Up regulation	MAPK, PI3K-AKT, p53, ErbB	I, II/107	Nadal et al. [2015]
	miR-200b	Up regulation	MAPK, PI3K-AKT, p53, ErbB	I, II/107	Nadal et al. [2015]
Breast	miR-21	Up regulation	PDCD4, HIF1A	17	Qi et al. [2009]
	miR-10b	Up regulation	HOXD10	23	Ma et al. [2007]
	miR-155	Up regulation	SOCS1, FOXO3	15	Jiang et al. [2010]
	miR-373	Up regulation	CD44	11	Huang et al. [2008]
	miR-520c	Up regulation	CD44	11	Huang et al. [2008]
	miR-125b	Up regulation	EPO, EPOR	42	Ferracin et al. [2013]; van Schooneveld et al. [2015]
Liver	miR-18	Up regulation	-	22	Murakami et al. [2006]
	miR-20	Up regulation	-	22	Murakami et al. [2006]
	miR-195	Down regulation	-	22	Murakami et al. [2006]
	miR-21	Up regulation	-	20	Li et al. [2009]
	miR-101	Down regulation	-	20	Li et al. [2009]
	miR-92	Up regulation	-	4	Connolly et al. [2008]
Ovarian	miR-21	Up regulation	-	38	Resnick et al. [2009]
	miR-155	Down regulation	-	38	Resnick et al. [2009]
	miR-30c-1-3p	Up regulation	-	24	Häusler et al. [2010]
	miR-342-3p	Down regulation	-	24	Häusler et al. [2010]
	miR-16	Up regulation	-	35	Suryawanshi et al. [2013]
	let-7f	Down regulation	-	360	Zheng et al. [2013]
Oral	miR-21	Up regulation	-	60	Zahran et al. [2015]
	miR-184	Up regulation	-	60	Zahran et al. [2015]
	miR-145	Down regulation	-	60	Zahran et al. [2015]
	miR-26a	Down regulation	TMEM184B	36	Fukumoto et al. [2015]
	miR-26b	Down regulation	TMEM184B	36	Fukumoto et al. [2015]
	miR-375	Down regulation	-	51	Lajer et al. [2011]
	miR-31	Up regulation	-	51	Lajer et al. [2011]
Glioblastoma	miR-23	Up regulation	Mdm2, TSC1	Cell line	Tang et al. [2011]
	miR-10b	Up regulation	HOXD10, RhoC	20	Guessous et al. [2013]
	miR-25	Up regulation	Mdm2, TSC1	9/I, III	Ciafre et al. [2005]
	miR-16	Up regulation	BCL2	Cell line	Chaudhry et al. [2010]
	miR-19a	Up regulation	-	118	Jia et al. [2013]
	miR-451	Down regulation	PI3K/AKT	Cell line	Gal et al. [2008]
	miR-145	Down regulation	Oct4, SOX2	Cell line	Koo et al. [2012]
Retinoblastoma	miR-373	Up regulation	-	3	Yang and Mei, 2015]
	miR-181a	Down regulation	CDKN1B	3	Yang and Mei, 2015]
	miR-125b	Down regulation	CDK6, CDC25A	3	Yang and Mei, 2015]
	let-7b	Down regulation	CDK6, CDC25A	3	Yang and Mei, 2015]
	miR-25	Up regulation	BCL2L1	3	Yang and Mei, 2015]
	miR-18a	Up regulation	BCL2L1	3	Yang and Mei, 2015]
	miR-20a	Up regulation	BCL2L1	3	Yang and Mei, 2015]
Prostate	miR-141	Up regulation	-	102	Kelly et al. [2015]
	miR-145	Up regulation	-	102	Kelly et al. [2015]
	miR-155	Up regulation	-	102	Kelly et al. [2015]
	let7a	Down regulation	-	102	Kelly et al. [2015]
	miR-375	Up regulation	-	102	Kelly et al. [2015]
Colon	let-7	Down regulation	KRAS	Cell line	Graziano et al. [2010]
	miR-29	Down regulation	MMP2, DNMT3A/B	Cell line	Ding et al. [2011]
	miR-30a-5P	Down regulation	DTL	Cell line	Baraniskin et al. [2012]
	miR-34a	Down regulation	FRA1, SIRT1, MYC, BCL2	Cell line	Schetter et al. [2012]
	miR-17-92 cluster	Up regulation	E2F1	Cell line	Yu et al. [2012]
	miR-95	Up regulation	SNX1	Cell line	Huang et al. [2011]
	miR-135a/b	Up regulation	APC	Cell line	Luo et al. [2011]
Gastric	miR-21	Up regulation	RECK	59/I, II, III, IV	Zhang et al. [2008]; Tsujiura et al. [2010]; Zheng et al. [2010]
	miR-17-5p	Up regulation	-	87/I, II, III, IV	Tsujiura et al. [2010]; Wang et al. [2012]
	miR-1	Up regulation	MET	116/I, II, III, IV	Liu et al. [2011]
	miR-421	Up regulation	-	141/I, II, III, IV	Zhou et al. [2012]; Wu et al. [2014]
	miR-34	Up regulation	MET	141/I, II, III, IV	Zhou et al. [2012]; Wu et al. [2014]
	miR-195-5p	Down regulation	-	In vivo	Gorur et al. [2013]
	miR-196a	Down regulation	-	In vivo	Tsai et al. [2012]
	miR-203	Down regulation	Annexin A1, HMGA2, HOXA8	130/I, II, III, IV	Imaoka et al. [2015]
	let-7a	Down regulation	EMT activators	69/I, II, III, IV	Arabpour et al. [2016]
Hepatocellular carcinoma	miR-373	Up regulation	PPP6C	110	Wu et al. [2011]
	miR-381	Up regulation	-	110	Murakami et al. [2013]

(Continued)

TABLE I. (Continued)

Type of cancer	miRNA	Expression in cancer	Target gene	Stage/patient sample	Citation
	miR-130b	Up regulation	TP53INP1	57	Liu et al. [2012]; Wei et al. [2013]
	miR-20a	Up regulation		110/I, II, III	Fan et al. [2013]; Wei et al. [2013]
	miR-21	Up regulation	C/EBPb, RhoB, PDCD4, PTEN	137/I, II, III	Ura et al. [2009]; Xu et al. [2011]; Wei et al. [2013]; Zhou et al. [2011]
	miR-122	Down regulation	c-Myc, Bcl-w, ADAM-1, Wnt-1, MTTP	90/B, C, D, A	El-Garem et al. [2014]
	miR-223	Down regulation	STMN1	110/I, II, III	Ura et al. [2009]; Xu et al. [2011]; Wei et al. [2013]; Zhou et al. [2011]

genes could contribute to cancer initiation and progression. In respect to the magnitude of miRNA genes in the pathogenesis and progression of cancer, the utilization of suitable methods for assessing miRNAs provide insight into new opportunities for cancer

treatment by modulating miRNA pathways and activities [Lee et al., 2008; Hernandez et al., 2013].

There are various conventional miRNA detection strategies including microarray, RT-PCR, and Northern blotting. Conventional

TABLE II. Various Techniques for Detecting MiRNAs in Cancer

Technique	miRNA	Type of cancer	Expression in cancer	Citation
BLI	miR-21	Breast	Up regulation	Hernandez et al. [2013]
	miR-221	Papillary thyroid carcinoma	Up regulation	Kim et al. [2008]
	miR-9	Embryonic carcinoma	Down regulation	Ko et al. [2008]
	miR-9	Embryonic carcinoma	Down regulation	Ko et al. [2008]
	miR-124a	Embryonic carcinoma	Up regulation	Ko et al. [2009a]
	miR-155	Lung	Up regulation	Yao et al. [2012]
	miR-10b	Breast	Up regulation	Yigit et al. [2013]
	miR-10b	Adenocarcinomas	Up regulation	Yigit et al. [2013]
	miR-1	-	Up regulation	Kang et al. [2015]
	miR-26a	-	Down regulation	Kang et al. [2015]
MB	miR-124a	-	Up regulation	Kang et al. [2015]
	miR-126	-	Up regulation	Kang et al. [2015]
	miR-206	-	Up regulation	Kang et al. [2015]
	miR-221	-	Up regulation	Kang et al. [2015]
	miR-9	-	Down regulation	Kang et al. [2015]
	miR-136	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
	miR-147	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
	miR-1250	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
	miR-148a	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
	miR-632	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
Microarray	miR-646	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
	miR-668	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
	miR-877	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
	miR-503	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
	miR-220a	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
	miR-323-5p	Oral cancer	Down regulation	Momen-Heravi et al. [2014]
	miR-24	Oral cancer	Up regulation	Momen-Heravi et al. [2014]
	miR-27b	Oral cancer	Up regulation	Momen-Heravi et al. [2014]
	let-7 family	Breast	Down regulation	Litman et al. [2007]
	miR-21	Breast	Up regulation	Litman et al. [2007]
	miR-505-5p	Breast	Down regulation	Matamala et al. [2015]
	miR-125b-5p	Breast	Down regulation	Matamala et al. [2015]
	miR-21-5p	Breast	Up regulation	Matamala et al. [2015]
	miR-96-5p	Breast	Up regulation	Matamala et al. [2015]
	miR-576-5p,	Glioblastoma	Up regulation	Dong et al. [2014]
	miR-340	Glioblastoma	Up regulation	Dong et al. [2014]
	miR-626	Glioblastoma	Up regulation	Dong et al. [2014]
	miR-320	Glioblastoma	Down regulation	Dong et al. [2014]
	let-7g-5p	Glioblastoma	Down regulation	Dong et al. [2014]
	miR-7-5P	Glioblastoma	Down regulation	Dong et al. [2014]
RT-PCR	miR-223	Gastric	Up regulation	Gorur et al. [2013]
	miR-106b	Gastric	Up regulation	Gorur et al. [2013]
	miR-147	Gastric	Up regulation	Gorur et al. [2013]
	miR-34a	Gastric	Up regulation	Gorur et al. [2013]
	miR-130b	Gastric	Up regulation	Gorur et al. [2013]
	miR-638	Gastric	Down regulation	Gorur et al. [2013]
	miR-37	Gastric	Down regulation	Gorur et al. [2013]
	miR18a	Colon	Up regulation	Giráldez et al. [2013]
	miR19a	Colon	Up regulation	Giráldez et al. [2013]
	miR15b,	Colon	Up regulation	Giráldez et al. [2013]
NGS	miR29a	Colon	Up regulation	Giráldez et al. [2013]
	miR-574-3p	Breast	Down regulation	Krishnan et al. [2015]
	miR-660-5p	Breast	Down regulation	Krishnan et al. [2015]

BLI: bioluminescence imaging, MB: molecular beacon, NGS: Next Generation Sequencing, RT-PCR: Reverse transcription polymerase chain reaction.

detection methods are associated with some limitations which indicate a necessity for devising and deploying high-throughput noninvasive repetitive and real-time imaging systems for the detection of miRNAs in preclinical and clinical settings [German et al., 2008; Ko et al., 2009a; Sun et al., 2010]. In the following section, we will describe recently developed miRNA imaging strategies such as the various bioluminescence systems, fluorescent imaging approaches, as well as magnetic resonance imaging. In addition, both the advantages and inherent inefficiencies of various imaging systems are also described.

Recent significant advancement in reporter-based optical imaging systems has provided the opportunities of noninvasive and repeated real-time analysis of the miRNA gene expression in living cells. These miRNA imaging approaches offer a better elucidation of the biogenesis and biological function of miRNAs in vivo as well as miRNAs expression profile in human diseases [Gambhir et al., 1999; Blasberg, 2003; Wang et al., 2003]. These imaging techniques could, for example, provide better data on intact biological context than the “snapshots” provided by in vitro assays [Lee et al., 2008; Hernandez et al., 2013].

Several studies indicated that there are different categories for miRNA imaging. One of the main categories is based on nanoparticles, Bioluminescent imaging (BLI), fluorescent proteins (FPs), and molecular beacon (MB) imaging.

Despite of much advancement in the field of imaging for detecting of miRNAs, this field is still in its infancy. Modern and new imaging techniques provide a new horizon for the study of various targets and molecules in different levels in living cells [Ottobri et al., 2006; Lee et al., 2008; Hernandez et al., 2013].

Some studies have been used bioluminescent reporter proteins such as Firefly luciferase (Fluc) and Gaussia luciferase (Gluc) for the imaging of various miRNAs in living cells [Ottobri et al., 2006]. Gaussia luciferase utilizes coelenterazine as a substrate and emits light with a peak at 480 nm with a broad spectrum extending to 600 nm. Firefly luciferase emits light with a peak at 562 nm. D-luciferin serves as a good substrate for Firefly luciferase [Gould and Subramani, 1988; Tannous et al., 2005].

Other systems are reporter-based miRNA detection imaging systems. In the presence of miRNA, these systems demonstrate a dropping in reporter signals which is correlated with translational repression of its target mRNA [Ko et al., 2008, 2009b; Kim et al., 2009]. These imaging systems could facilitate potential applications for assessing of miRNA levels during biological processes such as cell growth and differentiation and the cell cycle in living animals [Ko et al., 2009b]. For instance, these techniques could be utilized to detect and monitor differentiation patterns of stem cells by miRNA (cell-specific) expression in vivo or to detect miRNAs involved in cancer progression, for example, miR-221 and miR-21 [Ko et al., 2009b]. Table II represents a variety of miRNAs which are detected by various techniques.

## CONCLUDING REMARKS

MicroRNAs are a class of small non-coding RNA species, known as miRNAs, which control gene expression across various physiological and pathological processes. Their aberrant expression may be involved

in human diseases. Among human diseases, it has been shown that miRNAs are aberrantly expressed or mutated in cancer, indicating that they may play a role as a new class of oncogenes or tumor suppressor genes. As the miRNA field continues to grow and evolve, it is an important step to develop efficient tools for rapid, specific, sensitive, and noninvasive imaging detection of miRNAs toward understanding the functions of miRNAs in various regulatory pathways in vivo, which consequently effect on the development of miRNA-based diagnostic and therapeutic assays at molecular level and new targets in drug discovery. In contrast to conventional imaging systems, new molecular imaging systems such as reported-based optical imaging systems are multiplex and have high specificity against other family RNAs and minimum sample manipulation and could be utilized for studying living systems. However, once new generations of imaging systems (i.e., reporter-based imaging) involve genetic modification in studied subjects; there are still some concerns regarding their translation into clinical practice. In conclusion, molecular imaging techniques are robust tools for high-throughput noninvasive repetitive and real-time monitoring of biogenesis, localization patterns, and biological function of miRNAs in vivo as well as miRNAs expression profile in human diseases particularly cancer. Such imaging systems will deepen our knowledge of miRNAs expression patterns and their biological functions in various tumorigenic regulatory networks in vivo, which eventually effect on the development of miRNA-based diagnostic and therapeutic assays and new targets in cancer drug discovery.

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